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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/070,789	08/06/2002	C Frank Bennett	RTSP-0280	9486

7590 12/27/2004

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EXAMINER	
CHONG, KIMBERLY	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 12/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/070,789	BENNETT ET AL.	
	Examiner	Art Unit	
	Kimberly Chong	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-20 is/are pending in the application.

4a) Of the above claim(s) 1-14 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 15-20 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 3/6/02
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

I. Claims 1-14 are drawn to antisense compounds targeted to human X-linked inhibitor of apoptosis (XIAP).

II. Claims 15-20 are drawn to methods of inhibiting the expression of human XIAP and to methods of treating a human comprising the use of antisense compounds targeted to human XIAP.

Under PCT Rule 13.2 the requirement of unity of invention referred to in PCT Rule 13.1 shall be fulfilled only when there is a special technical relationship among those inventions involving one or more of the same or corresponding special technical features.

Claim 3 specifically claims antisense SEQ ID NOS: 8-21 and 23-45, which are targeted to and modulate the expression of gene human X-linked inhibitor of apoptosis (XIAP). This application does not comply with the requirements of unity of invention (Rules 13.1, 13.2, and 13.3) for the reasons indicated below:

According to the guidelines in Section (f)(i)(a) of Annex B of the PCT Administrative Instructions, the special technical feature as defined by PCT Rule 13.2 shall be considered to be met when all the alternatives of a Markush-group are of

similar nature. For chemical alternatives, such as the claimed antisense sequences, the Markush group shall be regarded as being of similar nature when (A) all alternatives have a common property or activity and (B)(1) a common structure is present, i.e. a significant structure is shared by all of the alternatives or (B)(2) in cases where the common structure cannot be the unifying criteria, all alternatives belong to an art recognized class of compounds in the art to which the invention pertains.

The instant antisense sequences are considered to be each separate inventions for the following reasons: the sequences do not meet the criteria of (A), common property or activity or (B)(2), art recognized class of compounds. Although the sequence target and modulate expression of the same gene, each antisense sequence behaves in a different way in the context of the claimed invention. Each sequence targets a different and specific region of gene Y and each sequence modifies (either increases or decreases) the expression of the gene to varying degrees (per Applicants' Table 1 in the specification). Each member of the class cannot be substituted; one for the other, with the expectation that the same intended result would be achieved.

Further, although the sequences target the same gene, the sequences do not meet the criteria of (B)(1), as they do not share, one with another, a common core structure. Accordingly, unity of invention between the antisense sequences is lacking and each antisense sequence claimed is considered to constitute a special technical feature.

Additionally, claim 1 does not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, it lacks the same or corresponding

special technical feature for the following reason: claim 1 is drawn to an antisense compound targeted to a nucleic acid molecule encoding human XIAP that specifically hybridizes to human XIAP, which is the special technical feature. Liston et al. (Nature 379 (6563), 349-353 1996, figure 3 pg. 352) teaches an oligonucleotide that specifically hybridizes to a human XIAP. Since the specific probe taught in Liston et al. meets the structural limitations of claim1, it therefore is considered to inherently meet the functional limitations of claim 1, namely inhibit the expression of human XIAP. Thus, antisense to XIAP was known in the prior art and so cannot constitute a special technical feature.

During a telephone conversation with Jane Massey Licata on 10/29/2004, a provisional election was made with traverse to prosecute the invention of claims 15-20. It was requested that applicants specify a specific human XIAP sequence to facilitate the search. Therefore, a provisional election was made with traverse to prosecute human XIAP having SEQ ID NO:1. Affirmation of this election must be made by applicant in replying to this Office action. Claims 1-14 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claim Objections

Claims 15 and 16 are objected to because of the following informalities: The instant claims are objected to as dependent on a non-elected claim. This objection can be overcome if all the limitations of claim 1 are incorporated into the instant claims. Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Korneluk *et al.* (U.S. Patent Number 6,133,437) in view of Baracchini *et al.* (U.S. Patent Number 5,801,154) and Milner *et al.* (Nature Biotechnology 15: 537-541, 1997).

The instant claim is drawn to a method of inhibiting the expression of XIAP in human cells or tissues comprising contacting the cells or tissues with an antisense compound targeted to a nucleic acid molecule that encodes XIAP.

Korneluk *et al.* teaches a method of inhibiting the expression of the family members of IAP, including XIAP (see column 5, line 32) and further teaches the sequence of the XIAP gene (see column 4, line 57 and Example 9, column 26). Korneluk *et al.* teaches that the skilled artisan can screen for antisense compounds that may be selective for XIAP (see column 4, line 60). Korneluk *et al.* does not teach a specific antisense embodiment by a particular structure or length.

Baracchini *et al.* teach that antisense oligonucleotides are preferably 8 to 30 nucleotides in length (see column 8, line 57).

Milner *et al.* teaches a screening assay for the selection of an antisense RNA targeted to a particular gene (see experimental protocol, pg 541).

It would have been obvious to one of ordinary skill in the art to make antisense of the length 8-30 as taught by Baracchini *et al.*, to the nucleic acid encoding XIAP to be used in a method of inhibiting XIAP in cells *in vitro*, as taught by Korneluk *et al.*, and further, using a method of screening for antisense compounds targeted to a nucleic acid encoding XIAP, as taught by Milner *et al.*

One would have been motivated to use antisense compounds of a length of 8-30 to human XIAP in a method of inhibiting XIAP in cells *in vitro*, as taught in Korneluk *et al.* One would have been motivated to use antisense compounds of the preferred length of 8 to 30 nucleotides, and use them in a method of inhibiting in cells *in vitro*, as taught in Korneluk *et al.*, because they are less expensive to make, provide greater cellular uptake and have greater target affinity, and further this length is the convention in the art, as exemplified by Baracchini *et al.*

Finally, one would have a reasonable expectation of success given that Korneluk *et al.* teach a method of inhibiting IAP in cells by administering an antisense compound targeted to a nucleic acid encoding IAP and, since Baracchini *et al.* teach the preferred length of an antisense is 8 to 30 nucleotides. Further, one would have a reasonable expectation of success given that Milner *et al.* teach a screening assay for selecting an antisense compound targeted to the XIAP gene. Therefore at the time of the invention, inhibiting cells *in vitro* was routine to one of ordinary skill in the art.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 16 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 16 recites the limitation "said animal" in the claim. There is insufficient antecedent basis for this limitation in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 15 claims a method of inhibiting the expression of XIAP in human cells or tissues by administration of an antisense compound targeted to a nucleic acid encoding XIAP. Claim 16 claims a method of treating a human having a disease or condition associated with XIAP by administering an effective amount of antisense compound to inhibit XIAP expression. Claim 17 limits claim 16 by stating the disease or condition is a hyperproliferative disorder and claim 18 further limits claim 1 by stating the

hyperproliferative disorder is cancer. Claims 19 and 20 limit claim 16 by stating the disease or condition is follicular atresia and an inflammatory disorder.

Example 16 of the specification as filed teaches antisense to one variant of human XIAP and inhibition of human XIAP mRNA *in vitro* after treatment with the antisense compound. However, the claims are drawn to methods of inhibiting using antisense targeted to many variants of human XIAP. The specification as filed does not teach antisense to the broad genus of human XIAP genes as necessary to allow one skilled in the art to envisage a sufficient number of species of antisense required for the claimed methods of inhibition of expression of human XIAP and methods of treating a disease associated with expression of human XIAP.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

MPEP 2163 states in part, "An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004) (The patent at issue claimed a method of selectively inhibiting PGHS-2 activity by administering a non-steroidal compound that

selectively inhibits activity of the PGHS-2 gene product, however the patent did not disclose any compounds that can be used in the claimed methods. While there was a description of assays for screening compounds to identify those that inhibit the expression or activity of the PGHS-2 gene product, there was no disclosure of which peptides, polynucleotides, and small organic molecules selectively inhibit PGHS-2. The court held that "[w]ithout such disclosure, the claimed methods cannot be said to have been described.")

Thus, the instantly claimed invention cannot be said to have been adequately described in a way that would convey with reasonable clarity to those skilled in the art that, as of the filling date sought, applicant was in possession of the claimed invention because the claims in view of specification, while providing information on an antisense compound targeted to one variant of human XIAP, does not provide any other information or guidance as to what the structure of antisense targeted to other forms of human XIAP is necessary to practice the methods of inhibition of XIAP or treatment of a disease or condition associated with XIAP.

Claims 15-20 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibition of human x-linked inhibitor of apoptosis (XIAP) expression *in vitro* using antisense compounds, does not reasonably provide enablement for antisense-mediated inhibition of XIAP expression *in vivo*, or for methods of treating diseases associated with its expression *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with these claims.

The instant claims are drawn to methods of inhibiting the expression of human XIAP in human cells or tissues comprising contacting human cells or tissues with an antisense compound (SEQ ID No. 8). Further, the claims are drawn to a method of treating a human having a disease or condition associated with XIAP, namely cancer, follicular atresia or an inflammatory disorder, comprising administering an effective amount of the antisense compound (SEQ ID No. 8) so that expression of human XIAP is inhibited and treatment effects are provided. Example 16 of the specification as filed teaches inhibition of human XIAP mRNA *in vitro* after treatment with an antisense compound (SEQ ID No. 8).

There is no guidance in the specification as filed that teaches how to target the claimed antisense compound to specific the human cell or tissues, inhibit the expression of human XIAP *in vivo*, and further provide treatment for cancer, follicular atresia or an inflammatory disorder. Although the specification discloses general methodologies of using the claimed antisense compound *in vivo* or in methods of treatment, such a disclosure would not be considered enabling since the state of antisense-mediated gene inhibition is highly unpredictable.

The following factors have been considered in the analysis of enablement: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the level of one of ordinary skill, (5) the level of predictability in the art, (6) the amount of direction provided by the inventor, (7) the existence of working examples, (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The claimed breadth of claims 15-20 encompass methods of treating a broad range of diseases in different tissues by use of an antisense targeted to human XIAP gene *in vivo*. Although the specification teaches inhibition of human XIAP mRNA *in vitro* after treatment with an antisense compound (see example 16), this guidance is not sufficient to resolve the known unpredictability in the art associated with appropriate *in vivo* delivery and treatment effects provided by the instantly claimed methods.

The references cited herein illustrate the state of the art for therapeutic *in vivo* applications using antisense compounds. Branch stresses that "because it is very difficult to predict what portions of an RNA molecule will be accessible in vivo, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells" (TIB 23: 45-50 1998). Green *et al.* states that "[i]t is clear from the evolution of antisense technology from a laboratory research tool into a mechanism for designing active and effective drugs is far from complete. Although there is little doubt that systemically administered antisense [oligonucleotides] can inhibit the expression of specific genes in patients, the effectiveness of such therapy in modifying the course of a particular illness has not yet been established. In addition, toxicity in humans appears more problematic than might be predicted based on preclinical studies in rodents. Clearly, additional work must be done to unravel the complex problems associated with drug delivery, mRNA targeting and aptameric, nonantisense effects" (Antisense Therapy in Human Disease; Vol. 191, No. 1 2000, pg 103 column 2).

The problems with efficient delivery of antisense oligonucleotides to cells has been addressed by Jen *et al.*, who states that "[o]ne of the major limitations for the therapeutic use of AS-ODNS ...is the problem of delivery....presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable (Stem Cells 2000; 18:307-319 pg 315 column 2)." Jen *et al.* concludes that "[g]iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive (see p 315, second column)."

As outlined above, it is well known that there is a high level of unpredictability in the antisense art for therapeutic *in vivo* applications. The scope of the claims in view of the specification as filed together do not reconcile the unpredictability in the art to enable one of skill in the art to make and/or use the claimed invention, namely treatment of cancer, follicular atresia or an inflammatory disorder by administration of an antisense compound (SEQ ID No. 8) targeted to a gene encoding human XIAP. While one skilled in the art may be able to find an antisense oligonucleotide targeted to a gene encoding human XIAP and demonstrate inhibition of human XIAP in cells *in vitro* after treatment with the antisense oligonucleotide, the specification as filed does not teach how to administer any antisense oligonucleotide to treat cancer, follicular atresia or an inflammatory disorder as claimed.

The specification as filed, specifically example 16, teach that administration of an antisense compound (SEQ ID NO. 8) showed that human XIAP expression was inhibited in cells *in vitro* (see Table 2). Nowhere in the specification does it teach that

because of the administration of this antisense compound that cancer, follicular atresia or an inflammatory disorder was treated *in vivo*. Crooke (Antisense Research and Application, Chapter 1, Springer-Verlag, New York. 1998) supports the difficulties of extrapolating from in vitro experiments and states on p. 3, paragraph 2, "extrapolations from *in vitro* uptake studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate and, in fact, there are now several lines of evidence in animals and man [that] demonstrate that, even after careful consideration of all *in vitro* uptake data, one cannot predict *in vivo* pharmacokinetics of the compounds based on *in vitro* studies [references omitted]."

Given the teachings of the specification as discussed above, one skilled in the art would not know *a priori* whether introduction of antisense oligonucleotides *in vivo* by the broadly disclosed methodologies of the instantly claimed invention, would result in successful inhibition of expression of a target gene. To practice the claimed invention, one of skill in the art would have to *de novo* determine; the stability of the antisense molecule *in vivo*, delivery of the antisense molecule to the whole organism, specificity to the target tissue *in vivo*, dosage and toxicity *in vivo*, and entry of the molecule into the cell *in vivo* and the effective action therein. Without further guidance, one of skill in the art would have to practice a substantial amount of trial and error experimentation, an amount considered undue and not routine, to practice the instantly claimed invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached at 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file

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